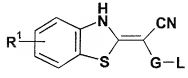
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1(Previously presented). A method for treating a metabolic disorder mediated by insulin resistance or hyperglycemia, comprising administering to a human or other mammal in need thereof an effective amount of a compound according to formula I



(I)

as well as a tautomer, geometrical isomer, optically active form as enantiomer, diastereomer, racemate, or a pharmaceutically acceptable salt thereof, wherein

G is a pyrimidinyl group;

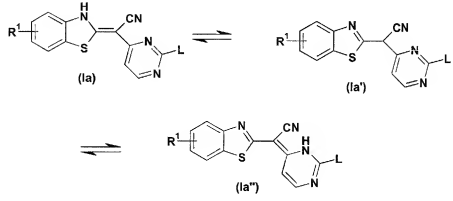
L is an C_1-C_6-alkoxy, an amino group, or a 3-8 membered heterocycloalkyl, containing at least one heteroatom selected from the group consisting of N, O, and S; and

R^1 is selected from the group consisting of hydrogen, sulfonyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl or C_1-C_6-alkoxy, aryl, halogen, cyano and hydroxy.

2(Previously presented). The method according to claim 1, wherein the metabolic disorder is diabetes type II.

3(Previously presented). The method according to claim 1, wherein, in the compound, R^1 is H or C_1-C_3 alkyl.

4(Previously presented). The method according to claim 1, wherein the compound has any of formulae (Ia), (Ia') or (Ia''):



wherein R^1 is selected from the group consisting of hydrogen, sulfonyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, aryl, halogen, cyano, and hydroxy; and

L is an amino group of the formula $-NR^3R^4$, wherein R^3 and R^4 are each independently from each other H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, aryl, heteroaryl, saturated or unsaturated 3-8-membered cycloalkyl, 3-8-membered heterocycloalkyl, (wherein said

cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups may be fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group), C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, C_1-C_6-alkenyl aryl, C_1-C_6-alkenyl heteroaryl, C_1-C_6-alkynyl aryl, C_1-C_6-alkynyl heteroaryl, C_1-C_6-alkyl cycloalkyl, C_1-C_6-alkyl heterocycloalkyl, C_1-C_6-alkenyl cycloalkyl, C_1-C_6-alkenyl heterocycloalkyl, C_1-C_6-alkynyl cycloalkyl, C_1-C_6-alkynyl heterocycloalkyl; or

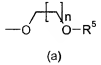
R^3 and R^4 may form a ring together with the nitrogen to which they are bound.

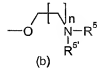
5(Previously presented). The method according to claim 4, wherein, in the compound, R^3 is hydrogen or a methyl or ethyl or propyl group and R^4 is selected from the group consisting of a (C_1-C_6)-alkyl, C_1-C_6- alkyl-aryl, C_1-C_6-alkyl-heteroaryl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, and 4-8 membered saturated or unsaturated cycloalkyl.

6(Previously presented). The method according to claim 4, wherein, in the compound, R^3 and R^4 form an optionally substituted piperazine or a piperidine or a morpholine or a pyrrolidine ring together with the nitrogen to which they are bound, whereby said optional substituent is selected from the group consisting of a C_1-

C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, aryl, heteroaryl, saturated or unsaturated 3-8-membered cycloalkyl, 3-8-membered heterocycloalkyl, (wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups may be fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group), C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, C_1-C_6-alkenyl aryl, C_1-C_6-alkenyl heteroaryl, C_1-C_6-alkynyl aryl, C_1-C_6-alkynyl heteroaryl, C_1-C_6-alkyl cycloalkyl, C_1-C_6-alkyl heterocycloalkyl, C_1-C_6-alkenyl cycloalkyl, C_1-C_6-alkenyl heterocycloalkyl, C_1-C_6-alkynyl cycloalkyl, and C_1-C_6-alkynyl heterocycloalkyl.

7 (Previously presented). The method according to claim 5, wherein, in the compound, L is selected from the group consisting of:


(a)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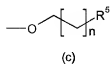
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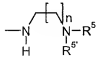
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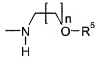
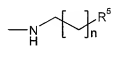

(e)


(f)

wherein n is 1 to 10, and

R^5 and $R^{5'}$ are independently selected from each other from the group consisting of H, C_1-C_{10} alkyl, aryl or hetero-aryl, C_1-C_6 alkyl-aryl, and C_1-C_6-alkyl-heteroaryl.

8(Previously presented). The method according to claim 1, wherein the compound is selected from the group consisting of:

1,3-benzothiazol-2-yl(2,6-dimethoxy-4-pyrimidinyl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(1H-imidazol-5-yl)ethyl]amino}-4-pyrimidinyl)acetonitrile;

1,3-benzothiazol-2-yl[2-(1-piperazinyl)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl[2-(4-benzyl-1-piperidinyl)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl[2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl[2-(4-morpholinyl)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl(2-{4-[2-(4-morpholinyl)ethyl]-1-piperazinyl}-4-pyrimidinyl)-acetonitrile;

1,3-benzothiazol-2-yl{2-[4-(benzyloxy)-1-piperidinyl]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl[2-(4-hydroxy-1-piperidinyl)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(dimethylamino)ethyl]amino}-4-pyrimidinyl)acetonitrile;

1,3-benzothiazol-2-yl[2-(dimethylamino)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-methoxyethyl)amino]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-hydroxyethyl)amino]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl[2-(propylamino)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl(2-{[3-(1H-imidazol-1-yl)propyl]amino}-4-pyrimidinyl)acetonitrile;

1,3-benzothiazol-2-yl[2-(1-pyrrolidinyl)-4-pyrimidinyl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-phenylethyl)amino]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(2-pyridinyl)ethyl]amino}-4-pyrimidinyl)acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-pyridinylmethyl)amino]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl{2-[4-(1H-1,2,3-benzotriazol-1-yl)-1-piperidinyl]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl{2-[4-(2-pyrazinyl)-1-piperazinyl]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl{2-[4-(2-pyrimidinyl)-1-piperazinyl]-4-pyrimidinyl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(3-pyridinyl)ethyl]amino}-4-pyrimidinyl)acetonitrile;

1,3-benzothiazol-2-yl(5-bromo-2-{[2-(dimethylamino)ethyl]amino}-4-pyrimidinyl)-acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-morpholin-4-ylethyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl[2-(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)-acetonitrile;

1,3-benzothiazol-2-yl(2-{methyl[3-(methylamino)propyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-4-yl)-acetonitrile;

1,3-benzothiazol-2-yl{2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(1-methyl-1H-imidazol-4-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(1H-indol-3-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(4-hydroxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

tert-butyl ({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)acetate

{2-[(3-aminopropyl)amino]pyrimidin-4-yl}(1,3-benzothiazol-2-yl)acetonitrile;

{2-[(2-aminoethyl)amino]pyrimidin-4-yl}(1,3-benzothiazol-2-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[3-(dimethylamino)propyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-piperidin-1-ylethyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(1-methyl-1H-imidazol-5-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl[2-(benzylamino)pyrimidin-4-yl]acetonitrile;

isopropyl 3-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)propanoate;

1,3-benzothiazol-2-yl{2-[(3-hydroxypropyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl{2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl{2-[(pyridin-4-ylmethyl)amino]pyrimidin-4-yl}acetonitrile;

tert-butyl 4-[2-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)-ethyl]phenylcarbamate;

(2-{[2-(4-aminophenyl)ethyl]amino}pyrimidin-4-yl)(1,3-benzothiazol-2-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(3-methoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(2-fluorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl[2-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-hydroxy-2-phenylethyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-{[3-(trifluoromethyl)pyridin-2-yl]amino}ethyl)amino]-pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(3-chlorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(3,4-dichlorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(4-methoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(4-methylphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(3-fluorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(4-phenoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(2-phenoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(4-bromophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(4-fluorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-[1,1'-biphenyl]-4-ylethyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl{2-[(2-{4-[hydroxy(oxido)amino]phenyl}ethyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[2-(1H-1,2,4-triazol-1-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl(2-{[3-(1H-pyrazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile;

4-[2-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide;

{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(1H-tetraazol-5-ylmethyl)amino]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl[2-(benzyloxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(4-pyridin-3-ylbenzyl)oxy]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl[2-(pyridin-4-ylmethoxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl[2-(pyridin-2-ylmethoxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl[2-(3-pyridin-2-ylpropoxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(4-methoxybenzyl)oxy]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl[2-(pyridin-3-ylmethoxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl{2-[2-(4-methoxyphenyl)ethoxy]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl[2-([1,1'-biphenyl]-3-ylmethoxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(3,4,5-trimethoxybenzyl)oxy]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl{2-[(3,4-dichlorobenzyl)oxy]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl[2-({3-[(dimethylamino)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl{2-[(1-oxidopyridin-3-yl)methoxy]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[4-(morpholin-4-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl{2-[(4-pyridin-2-ylbenzyl)oxy]pyrimidin-4-yl}acetonitrile;

1,3-benzothiazol-2-yl(2-{[4-(piperidin-1-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl[2-(4-methoxyphenoxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl[2-(4-butoxyphenoxy)pyrimidin-4-yl]acetonitrile;

{2-[4-(4-acetylpiperazin-1-yl)phenoxy]pyrimidin-4-yl}(1,3-benzothiazol-2-yl)acetonitrile;

[2-(4-methoxyphenoxy)pyrimidin-4-yl][5-(trifluoromethyl)-1,3-benzothiazol-2-yl]acetonitrile;

N-[2-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)ethyl]-4-chlorobenzamide;

1,3-benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)acetonitrile;

1,3-benzothiazol-2-yl[2-({4-[(4-methylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl[2-({4-[(4-benzyl-piperazin-1-yl)methyl]-benzyl}oxy)pyrimidin-4-yl]acetonitrile;

1,3-benzothiazol-2-yl(2-{[4-(piperazin-1-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile;

1,3-benzothiazol-2-yl[2-({4-[(4-formylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile;

[2-({4-[(4-acetylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl](1,3-benzothiazol-2-yl)acetonitrile;

(3H-Benzothiazol-2-ylidene)-{2-[4-(4-[1,2,4]oxadiazol-3-ylmethyl-piperazin-1-ylmethyl)-benzyloxy]-pyrimidin-4-yl}-acetonitrile;

4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazine-1-carboxylic acid methyl ester;

2-[4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazin-1-yl]-acetamide;

(2-{4-[4-(2-Amino-acetyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-(3H-benzothiazol-2-ylidene)-acetonitrile;

[4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazin-1-yl]-acetic acid methyl ester;

(3H-Benzothiazol-2-ylidene)-(2-{4-[4-(2-methoxy-ethyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-acetonitrile;

4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazine-1-carboxylic acid dimethylamide;

(3H-Benzothiazol-2-ylidene)-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-benzyloxy]-pyrimidin-4-yl}-acetonitrile; and

(3H-Benzothiazol-2-ylidene)-(2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-acetonitrile.

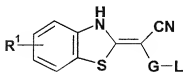
9(Previously presented). The method according to claim 1, wherein the compound further comprises at least

one supplementary drug selected from the group consisting of insulin, aldose reductase inhibitors, alpha-glucosidase inhibitors, sulfonyl urea agents, biguanides, thiazolidines, PPARs agonists, and GSK-3 inhibitors.

10(Previously presented). The method according to claim 9, wherein said supplementary drug is selected from the group consisting of a rapid acting insulin, an intermediate acting insulin, a long acting insulin, a combination of intermediate and rapid acting insulins, Minalrestat, Tolrestat, Sorbinil, Methosorbinil, Zopolrestat, Epalrestat, Zenarestat, Imirestat, Ponalrestat, ONO-2235, GP-1447, CT-112, BAL-ARI 8, AD-5467, ZD5522, M-16209, NZ-314, M-79175, SPR-210, ADN 138, or SNK-860, Miglitol, Acarbose, Glipizide, Glyburide, Chlorpropamide, Tolbutamide, Tolazamide, and Glimepriride.

11(Previously presented). The method according to claim 1, wherein n is 1 to 6.

12(Currently amended). A pharmaceutical composition comprising an ~~adjuvant, carrier, diluent, or excipient~~anti-diabetes agent and a compound according to formula I:



(I)

as well as a tautomer, geometrical isomer, optically active form as enantiomer, diastereomer,

racemate, or a pharmaceutically acceptable salt thereof,

wherein

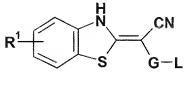
G is a pyrimidinyl group;

L is an C_1-C_6-alkoxy, an amino group, or a 3-8 membered heterocycloalkyl, containing at least one heteroatom selected from the group consisting of N, O, and S; and

R^1 is selected from the group consisting of hydrogen, sulfonyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl or C_1-C_6-alkoxy, aryl, halogen, cyano and hydroxy.

13 (Previously presented). A method for the treatment of a metabolic disorder mediated by insulin resistance or hyperglycemia, comprising administering an effective amount of the pharmaceutical composition according to claim 12 to a human or other mammal in need thereof.

14 (Currently amended). A method for the preparation of a pharmaceutical composition for the treatment of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising combining a compound with an ~~adjuvant, carrier, diluent, or excipient~~ anti-diabetes agent, wherein the compound is one according to formula I:



(I)

as well as a tautomer, geometrical isomer, optically active form as enantiomer, diastereomer, racemate, or a pharmaceutically acceptable salt thereof, wherein

G is a pyrimidinyl group;

L is an C_1-C_6-alkoxy, an amino group, or a 3-8 membered heterocycloalkyl, containing at least one heteroatom selected from the group consisting of N, O, and S; and

R^1 is selected from the group consisting of hydrogen, sulfonyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl or C_1-C_5-alkoxy, aryl, halogen, cyano and hydroxy.

15 (Previously presented). The method according to claim 1, wherein the metabolic disorder is inadequate glucose tolerance.

16 (Previously presented). The method according to claim 1, wherein the metabolic disorder is insulin resistance.

17 (Previously presented). The method according to claim 1, wherein the metabolic disorder is obesity.

18 (Previously presented). The method according to claim 1, wherein the metabolic disorder is polycystic ovary syndrome.

19 (Previously presented). The method according to claim 13, wherein the metabolic disorder is selected from the group consisting of diabetes type II, inadequate glucose

tolerance, insulin resistance, obesity, and polycystic ovary syndrome.

20(Previously presented). The method according to claim 14, wherein the metabolic disorder is selected from the group consisting of diabetes type II, inadequate glucose tolerance, insulin resistance, obesity, and polycystic ovary syndrome.